



## King's Research Portal

DOI:

[10.1177/0961203320928421](https://doi.org/10.1177/0961203320928421)

*Document Version*

Peer reviewed version

[Link to publication record in King's Research Portal](#)

*Citation for published version (APA):*

Bearne, L. M., Bieles, J., Georgopoulou, S., Andrews, J., Tully, A., Stolarchuk-Prowting, K., Williamson, T., Santana Suarez, B., Nel, L., D'Cruz, D., & Lempp, H. (2020). Fatigue in adults with primary Antiphospholipid Syndrome: findings from a mixed methods study. *Lupus*, 29(8), 924-933.  
<https://doi.org/10.1177/0961203320928421>

### **Citing this paper**

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

### **General rights**

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

### **Take down policy**

If you believe that this document breaches copyright please contact [librarypure@kcl.ac.uk](mailto:librarypure@kcl.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.

## **Fatigue in adults with primary Antiphospholipid Syndrome: findings from a mixed methods study**

### **ABSTRACT**

**Objective:** To explore the experience and impact of fatigue in adults with primary Antiphospholipid Syndrome (pAPS).

**Methods:** This sequential, explanatory mixed-methods study enrolled adults with  $\geq 6$ -month history of pAPS. Consenting participants completed the Functional Assessment of Chronic Illness Therapy–Fatigue subscale (FS), Multi-Dimensional Perceived Social Support Scale (MSPSS), Patient Health Questionnaire (PHQ9), Pittsburgh Sleep Quality Index (PSQI), International Physical Activity Questionnaire (IPAQMETS). Relationships between FS and other variables were explored with multiple linear regression. Interviews were conducted with a subgroup of participants and data analysed thematically.

**Results:** 103 participants were recruited (mean (Standard Deviation) 50.3 (10.1) years, 18 males). 62% of participants reported severe fatigue. Greater fatigue was associated with lower mood, physical inactivity, poorer sleep quality and lower perceived social support. The best-fit model explained 56% of the variance in FS (adjusted  $R^2=0.560$ ,  $F_{(3,74)}=33.65$ ,  $p>0.001$ ) and included PHQ9, and IPAQMETS as significant predictors, and PSQI as a non-significant predictor. Twenty participants completed interviews. Three key themes were identified: Characteristics of fatigue, Impact on life, Coping strategies.

**Conclusion:** Fatigue was a common symptom of pAPS and challenging to manage. Other factors, particularly mood and physical activity, influenced fatigue. Evidence-based self-management interventions are needed.

**KEY WORDS:** Antiphospholipid syndrome, fatigue, mixed methods

## INTRODUCTION

Antiphospholipid syndrome is an autoimmune, prothrombotic disorder, which occurs as a distinct clinical syndrome in isolation (primary antiphospholipid syndrome (pAPS)) or with other rheumatic and musculoskeletal diseases (RMDs) e.g. Systemic lupus erythematosus (SLE) [1]. The incidence of antiphospholipid syndrome is approximately 5/100,000 people annually and the prevalence is 40–50/100,000 people [1]. More women than men are affected (female:male ratio 5:1), and there is no racial prevalence for pAPS [2, 3]. Its clinical spectrum includes venous and/or arterial thromboses and pregnancy morbidity in the presence of antiphospholipid antibodies (e.g. lupus anticoagulant, anticardiolipin antibodies, anti- $\beta$ 2 glycoprotein-I antibodies). People with pAPS also experience other symptoms, such as fatigue, low mood and have difficulty keeping physically active [4, 5].

Chronic fatigue is an unpleasant, abnormal or excessive whole-body tiredness, disproportionate to or unrelated to activity or exertion and present for more than one month. It is not relieved easily by sleep or rest [6, 7]. Fatigue is a common symptom of RMDs and adversely affects an individual's health status, physical and social function. Studies in RMDs (e.g. Rheumatoid arthritis (RA) [8], SLE [9]) and other long-term conditions (e.g. Multiple Sclerosis [10]) have highlighted the impact and importance of fatigue [11-13].

The aetiology of fatigue is poorly understood. Theoretical models propose fatigue is a multi-causal, multi-dimensional symptom where disease-related (e.g. disease activity), cognitive/emotional (e.g. mood), physical and social factors (e.g. physical activity, social support) interact with each other [14-16]. In other RMDs, aspects outside the direct disease effects account for more of the variation of fatigue than condition-related features [15, 17, 18].

For this study, key factors which influence fatigue in other RMDs were identified. Low mood is common in people with RMDs and is consistently correlated with higher fatigue [16, 18, 19]. Low mood is also linked with sleep disturbance and evidence suggests that poor sleep quality influences fatigue levels [15, 20, 21]. Physical activity tends to be low in people with RMDs [22, 23] and physical inactivity is associated with higher fatigue [15, 24, 25]. This relationship may be mediated by mood, sleep or obesity [15, 24, 25]. Social support from family, friends or significant others (e.g. healthcare professionals) may also influence fatigue [16, 26].

Few studies have explored the experience and impact of fatigue in people with pAPS and it is rarely acknowledged in evidence-based management recommendations [27]. To inform the development of non-pharmacological interventions, a mixed-methods approach that comprises quantitative data to investigate the relationships between fatigue and key variables and qualitative data, to gain greater insight into these interactions and the experience and impact of fatigue is needed. This mixed-methods study aimed to explore the experience and impact of fatigue in adults with pAPS.

## **METHODS**

### **Study design**

This mixed-methods study adopted a sequential, explanatory design informed by the priority sequence model [28, 29]. In this model, an initial decision about the priority of a quantitative or qualitative method is taken; next, the sequence determines whether the complementary method serves either as a preliminary or as a follow-up phase. For this study, a cross-sectional survey was conducted to investigate relationships between fatigue and key psychosocial variables then, follow-up qualitative data were collected to explore the interactions identified in the quantitative phase and the direct experience and impact of fatigue in people with pAPS.

The study gained governance approval from North of Scotland Research Ethics Committee (14/NS/0026, 02/07/2014) and Research and Innovation from Guy's and St Thomas' Hospital NHS Foundation Trust (12/03/2015)

### **Quantitative phase**

#### **Participants and data collection**

Patients were eligible to be enrolled onto the study if they were: aged  $\geq 18$  years with pAPS (Sydney classification criteria [30]) for  $\geq 6$  months and had adequate verbal and written English language.

Patients who had other autoimmune rheumatic or inflammatory co-morbid conditions, malignancy, active chronic infections, current alcohol and/or drug abuse/dependence, Body Mass Index  $>30$  recorded in their medical records and/or were pregnant/breastfeeding, were excluded. Patients with positive antinuclear antibodies were also excluded as this may indicate APS secondary to other RMDs, such as SLE [31, 32].

Members of the direct care team reviewed the medical records of patients attending routine clinical appointments at a tertiary healthcare centre for the management of APS in the United Kingdom. Potentially suitable patients were identified and approached by the members of the direct care team to gauge their interest in the study and confirm their eligibility. Interested

participants received a questionnaire pack, which comprised study information, a consent form and six questionnaires to self-complete after their appointment. Alternatively, participants completed the questionnaires at home and returned them to the researchers in a pre-paid envelope. A researcher offered to support questionnaire completion after the clinical appointment or via telephone at a mutually convenient time. Patients who did not return the questionnaires were sent a second pack four-six weeks later. No further reminders were issued to non-responders.

### Sample Size

Using G\*Power software (version 3.1.9.2) a medium effect ( $f^2=0.15$ ,  $R^2=0.13$  equivalent) in variance of FS with  $p=0.05$ , a power of 0.80, and including four predictor variables required 89 participants.

**Sociodemographic and disease characteristics** including age, sex, birthplace, ethnicity, employment status (full-time, part-time, retired, unemployed, higher education, other), and disability registration (yes/no), duration of APS) were collected using a bespoke, self-administered questionnaire.

**Variables** Participants completed five self-completed, validated and standardised questionnaires.

**Fatigue** over the past week was measured using the 13-item Functional Assessment of Chronic Illness Therapy (FACIT-Fatigue Scale (FS, 4-point Likert scale ‘not at all fatigued’-‘very much fatigued’ with a lower score indicating greater fatigue (range 0-52). A score of  $<30$  indicates severe fatigue [33, 34].

**Mood** was assessed with the 9-item Patient Health Questionnaire (PHQ-9, 4-point Likert scale, ‘not at all’-‘nearly every day’) which is designed to correspond to the diagnosis of depression. A higher score indicates lower mood/depression (range 0-27) and scores  $\geq 10$  represents clinically depressive symptoms. [35, 36].

**Physical Activity** over the preceding 7 days was measured with the 4-item International Physical Activity Questionnaire – short form (IPAQ). The metabolic equivalent of task was calculated over seven days (METs/minutes/week – IPAQMETs) and scores  $\geq 600$  MET/minutes/week were considered physically active [37].

**The quality of sleep** over the past month was assessed using the 7-component Pittsburgh Sleep Quality Index (PSQI, 19-items, 4-point Likert scale ('not during the past month'-'three or more times a week')). A higher total PSQI score (range 0-21) represents lower sleep quality. A total PSQI score of >5 represents severe difficulties in at least 2 components [38, 39].

**Perceived social support** from family, friends and significant others was evaluated via the 12-item (7-point Likert scale ("strongly disagree"- "strongly agree")) Multi-Dimensional Perceived Social Support Scale (MSPSS) (range 1-7). Higher scores indicate higher perceived social support (1-2.9-low; 3-5-moderate; 5.1-7 high) [40, 41].

### **Qualitative phase**

A purposive sub-sample of participants enrolled to the cross-sectional survey were interviewed by one of two researchers (JA, SG) [42]. The interviewees varied in relation to most sociodemographic characteristics, APS type and lived experiences.

Interviewers were not directly involved in participants' healthcare and were supervised by an experienced qualitative researcher (HL). The audio-recorded interviews were conducted either face-to-face or by telephone, subject to participant's preference. A topic guide was developed *a priori* derived from other RMD fatigue literature [8, 9, 11] and refined with researchers' and patients' feedback to include questions aligned to the key quantitative variables. The semi-structured interview schedule allowed the interviewer to ask open-ended questions so the interviewee could diverge or expand the experiences or situations in more detail [43]. A pilot study was completed with three participants to assess comprehension and relevance of questions, timing and subjectively perceived research burden. No further changes were necessary to the interview guide (Table 1). Subtle judgement between interviewers and supervisor led to recruitment termination when data saturation of themes had been reached, e.g. no new information was reported by the participants [44].

### **Data Analysis**

#### **Statistical analysis**

Analyses were completed using SPSS statistics software v25.0 (IBM statistics Inc, Armonk, NY, USA). Statistical significance was set at  $p < 0.05$ . Frequencies and mean (standard deviation [SD]) values were reported for categorical and continuous descriptive variables, respectively. Relationships with FS (criterion variable) were explored using 2-tailed Spearman's Rho

correlation coefficients. A backward stepwise regression was performed including all measures associated with FS at  $P < 0.05$  in the bivariate analyses to determine whether they predicted the FS score. The model with the largest adjusted  $R^2$  model was used to perform a multiple linear regression analysis. Missing values were excluded pairwise. Univariate (Studentised residual values  $\pm 3SD$ ) and multivariate outliers (Mahalanobis distance  $p < 0.01$ ) were excluded, and models were evaluated for multicollinearity, normal and independent errors, and homoscedasticity.

### Qualitative data analysis

The interviews were anonymised, transcribed verbatim by one researcher and one professional transcribing agency, and the text analysed by two researchers (JA, HL) using the principles of Framework Analysis [45] via a five-stage structured approach [46] that included (i) familiarisation with text, (ii) coding within the qualitative computer package NVIVO 10 QSR International Pty Ltd. Version 10; 2014 [47] (iii) building categories and themes, (iv) identification of a thematic framework (v) linking findings with theoretical concepts.

Validation of data included (i) checking initial codes with one external researcher from one transcript; (ii) presentation of initial findings from the pilot study to supervisor (iii) discussing emerging themes from two additional transcripts and (iv) single counting. Transcript accuracy was checked by the participants against original recordings. A balanced reporting of data is a recognized validation strategy [47] therefore a range of accounts are presented, when available.

## RESULTS

### Quantitative phase

**Descriptive statistics:** 105 potentially eligible patients were approached between July 2014–June 2017. Two people with communication difficulties (hearing impairment ( $n=1$ ), insufficient English ( $n=1$ )) were excluded. 103 participants enrolled onto the study (18 males, mean age 50.3( $SD=10.1$ ) years). Data from 16 participants (10 male, 49.7( $10.1$ ) years) were omitted due to incomplete data. 87 participants (8 male, 50.3( $10.4$ ) years) were included in the analysis (Table 2).

62% of participants reported severe fatigue, 40% of participants reported depression, 24% of participants were classified as physically inactive, 69% participants revealed severe sleep difficulties and 35% participants reported low-moderate levels of perceived social support.

**Bivariate associations with fatigue:** FS was negatively associated with PHQ9 ( $r_s(84)=-0.750, p<0.001$ ) and PSQI ( $r_s(79)=-0.515, p<0.001$ ), and positively associated with IPAQMETS ( $r_s(81)=0.232, p=0.037$ ) and MSPSS ( $r_s(82)=0.239, p=0.030$ ) (Table 3).

**Multivariate analyses:** The backward stepwise regression included all variables (Table 4). The final best fit model explained 56% of the variance in FS, (adjusted  $R^2=0.560$ ,  $F_{(3,74)}=33.65$ ,  $p<0.001$ ) and included PHQ9 and IPAQMETS as significant predictors, PSQI as a non-significant predictor but not MSPSS (Table 5). Unstandardized beta coefficients indicated that for every unit increase in PHQ9 scores, FS decreased by 1.336 points (95% CI -1.72, -0.95, SE B=0.19,  $\beta=-0.67$ ,  $p<0.001$ ) and for every unit increase in IPAQMETS, FS increased by 0.001 points (95% CI 0.00004, 0.00119, SE B=0.0003,  $\beta=0.15$ ,  $p=0.037$ ). For every unit increase in PSQI scores, FS decreased by 0.286 points (95% CI -0.84, 0.27, SE B=0.28,  $\beta=-0.1$ ,  $p=0.306$ ).

## Qualitative phase

Twenty consenting participants were interviewed (duration: 20-60 minutes). The participants were all female and predominantly white (Table 2). Three key themes that were identified: (i) Characteristics of fatigue, (ii) Impact on life and (iii) Coping strategies, with two-four linked subthemes.

### 1) Characteristics of Fatigue

#### Use of Metaphors

All patients expressed experiencing fatigue at some time and used a range of metaphors to describe their fatigue, for example:

“fatigue hits you like a truck” (P7),

“I feel like a rag doll with no stuffing left”, (P1)

” I’m climbing up a really big hill with a massive rucksack on my back, and I’m struggling to get to the top” (P12)

“...[fatigue is] almost like a physical weight pulling me down feeling’ (P19)

#### Unpredictability and fluctuation of fatigue

Our participants (14/20) described that fatigue was unpredictable and variable and therefore interfered with their daily activities of living. They were uncertain about the causes or triggers for their fatigue.



‘You know the fatigue like I said is, it can happen any day and come out of the blue’. (P15)

‘So it’s very variable [fatigue], and it’s not even the fact that I’ve overdone it the day before. Which sometimes can help bring on the fatigue even more. But sometimes, umm, I’ve been absolutely fine, just been doing a steady pace for days, then boom it suddenly hits me and I’m in bed most of the day’. (P13)

#### Severity of fatigue

Many participants (17/20) commented on the severity of their fatigue and tended to rate this using a numerical scale or labels, such as ‘mild’, ‘manageable’, ‘bad ’ and ‘unbearable’ to convey the gravity of the fatigue.

‘.....‘I think my fatigue is, on a scale of one to ten, five at the most, three probably most of the time’. (P12)

‘I don’t know [how many times a week]. I have a couple really bad days a week’. (P19)

## **2) Impact on Life**

The impact of fatigue on each individual’s life was personal and wide ranging. All participants reported ‘low motivation’ or ‘forcing themselves’ to carry on with everyday life during periods of fatigue. Participants described the huge effort required to get through days when they were experiencing overwhelming fatigue and lack of energy.

#### Physical activity

Most participants (16/20) regarded themselves as physically active in their private and/or work lives, however, the frequency, intensity, duration and format of physical activity varied between interviewees. They were aware of the need to be active for their general health and were broadly aware of the public health recommendations.

‘I do, roughly, you know, between 15 and 20 minutes of walking a day...which is what the national, you know, erm...guidelines say’. (P15)

## Fatigue in pAPS\_mixed methods

They (16/20) described a relationship between physical activity and fatigue levels but noted that, at times, fatigue was a barrier to completing physical activity.

‘Sometimes it [my physical activity] will be morning, sometimes it will be the afternoon and sometimes early evening, it really depends. But usually sort of around one-ish.....I have to walk the dog’. (P6)

‘...when I did have bad fatigue periods, I couldn’t swim for a few weeks’ (P10)

Some participants (7/20) observed that exercise was a helpful management strategy for fatigue, at times.

‘...sometimes exercise can help fatigue, but I also know, and I can read my body quite well, when sometimes it is going to make me worse’ (P11)

‘...if I’m sedentary, it just makes it [fatigue] worse’ (P14)

### Quality of Sleep

Some participants (5/20) reported that sleep quality influenced their fatigue and that this was difficult to manage and frustrating.

‘A poor night’s sleep, makes me, it sort of extenuates tiredness, and it feels worse, and when my INR [International Normalised Ratio] is low’. (P14)

‘I hate it when I am so tired, for instance recently I been on holiday with a friend and I was determined not to do it [have a hour sleep during the day], but I’m afraid I did have to do it’. (P7)

### Impact of Mood

Some participants (8/20) described how mood and negative thoughts, affected their fatigue.

These thoughts could be intrusive and unhelpful, and this influenced their ability to accomplish their daily activities, for example.

‘...in some ways my mood can affect my fatigue, but it’s making me go more the other way at the moment, it’s making me feel like I can’t sleep... I’m constantly thinking about

things that are upsetting me or negative thoughts...and of course my body is getting tired, so by the time two days later I'm feeling more fatigued than I would have done if I hadn't been feeling so anxious and agitated' (P15)

A few participants (3/20) also reported that fatigue also influenced their mood.

'....I do believe that fatigue can trigger in me, slight depression, I'm not depressed by nature, but obviously the energy and dealing with it day in and day out when it [fatigue] is going on it is tiresome, and I find that your mind-set is not so clear, and you are not as rational as you would be, if you feel refreshed and positive'. (P11)

### Impact on Work

There was no doubt that fatigue impacted upon participants' salaried or daily work, which meant they had to make adaptations and were feeling unable to carry out complex tasks at times.

'[I] work flexi-time, so on a day where I just think I cannot do this anymore, I just need to get myself home, I can leave within reason'. (P10)

'.....I only work part time, whether I would be able to work full-time? I don't know the answer to that. Maybe I would get too fatigued if I worked full time'. (P6)

### 3) Coping strategies

All participants (20/20) employed a range of coping strategies to manage their fatigue. The strategies selected depended on the severity of the fatigue and were often informed by past successful experiences of dealing with their fatigue.

#### Individual coping strategies

Most patients (16/20) described how they applied individual coping strategies in their personal life, and pacing was a popular strategy.

'If I'm doing something that needs doing, and I start to get it [fatigue], I just carry on. I will suffer for it afterwards, but I don't want it [fatigue] to take over my life'. (P1)

'I think you have to pace, you have to be careful and you have to pace yourself, you can't do this, that and the other, and so, but even when you pace yourself you still get those times [of fatigue], for no reason, and you look at it and go, oh, it is like that today is it?' (P12)

#### Support from healthcare professionals

Many participants (19/20) had discussed fatigue with a healthcare professional, however, the topic of fatigue often received a mixed response by clinicians and tended not to be routinely reviewed.

‘I did obviously talk about it [fatigue] when I was first diagnosed, and they [clinicians] did take it seriously, but now there is not point keeping going on about it to them [clinicians]’ (P7)

‘when I spoke to my GP, my GP said ‘well you know more about this than I do.’ So I stopped at that point. But, although having said that, the rheumatologists that I saw when I had the problem with the steroids, he understood completely about the fatigue. Because he actually said to me, I told him about my symptoms with the joints in the muscles and things, he said to me ‘oh you must get so tired’ and I said ‘well it’s wonderful to hear someone actually say that I should be getting tired!’ (P7)

## DISCUSSION

This mixed-methods study is one of the first to explore the experience and impact of fatigue in adults with pAPS. The findings showed that fatigue was common, unpredictable and sometimes overwhelming in people with pAPS. It was influenced by factors such as low mood and physical inactivity. Participants had developed their own coping strategies to manage their fatigue and generally reported receiving high levels of social support. They reported minimal or variable understanding from health professionals.

Almost two thirds of our participants reported experiencing severe fatigue at times. Participants were vigilant about monitoring their fatigue so they could adopt strategies to mitigate the symptom. However, they found fatigue challenging to manage and difficult to explain to others, including health professionals. Consequently, participants used metaphors to express the character of fatigue and convey their increased effort and loss of energy, similar to people with long-term conditions such as SLE [9] or RA [11].

Over a third of our participants reported low mood and this was associated with higher fatigue levels. The relationship between mood and fatigue is well described in people with other long-term conditions [16, 48] and mood predicts fatigue even after adjustment for pain, and other potentially confounding variables in some RMDs [20]. Low mood can affect sleep and many of our participants reported sleep difficulties like people with other RMDs [15, 17, 20]. Sleep disturbances could be due to pain, stress or influenced by medication [17]. Whilst many interviewees described a clear link between fatigue and sleep, sleep quality did not independently predict fatigue in our quantitative data. This may be because sleep quality has an indirect effect

on fatigue and mediates the direct influence of depression or physical inactivity on fatigue [15] [17].

Over three quarters of our respondents reported meeting physical activity recommendations, which is higher than people with others RMDs [22, 23, 49]. This may be due to over-reporting because this data was collected using self-completed questionnaires, which is subject to recall bias. Alternatively, as many participants were employed or had active caring responsibilities, this finding may reflect activity undertaken for transportation (i.e. walking) related to their daily work. This study showed that greater physical activity was directly related to lower fatigue and some interviewees stated that physical activity/exercise was a helpful management strategy for fatigue. Brief, home-based physical activity and exercise interventions improve fatigue and sleep quality in people with RA, so this may be a promising intervention approach for people with pAPS [50, 51]. However, some interviewees found the physical activity hard to complete due to the unpredictability of fatigue so tailored strategies or interventions may be needed to accommodate fluctuations in fatigue.

Participants developed their own coping strategies, particularly pacing, to manage their fatigue. They mostly received good social support from family, friends and significant others (i.e. perceived emotional support), concurring with other research [52] and it is proposed that social support influences self-efficacy and has a buffering effect on fatigue [20, 26]. Whilst social support correlated with fatigue in our study, it did not independently explain the variance in fatigue in our multivariate analyses and exploration of the other types of perceived social support (i.e. instrumental (practical support such as housework) or informational (i.e. education) support) may clarify this relationship [52]. Informational social support could be provided by clinicians although our participants commented that fatigue was not regularly discussed in consultations. This could be because clinicians do not recognise the presence or impact of fatigue in people with pAPS or because it is not acknowledged in management recommendations [27]. Alternatively, the lack of evidence-based management strategies for fatigue in pAPS may mean that it is rarely a treatment focus. A multidisciplinary team approach may optimise the management of pAPS, similar to other RMDs, such as RA [53-55].

The conceptual model of fatigue for patients with RA by Hewlett et al. 2011 aligns with our findings [14]. Factors, such as pAPS itself; cognitive and behavioural dimensions (e.g. mood, physical activity) and personal aspects (e.g. social support) play a dynamic role in the experiences of fatigue and how people cope with it. This model may help researchers, clinicians and patients clarify the focus for future interventions, measurements, inform treatment and self-management.

This study has several strengths. The mixed methodology approach facilitated the integration of the findings from both phases within a single study. The findings are complementary and provide a deeper insight of the experience of fatigue in adults with pAPS [28, 29].

Our eligibility criteria were robust and adults with co-morbidities known to influence fatigue (e.g. obesity) were excluded to minimise confounding factors. The number of medical records reviewed and reasons for patients' ineligibility following review of medical notes were not documented. However, the team enrolled a range of participants with pAPS and only two potentially suitable patients, who were identified and approached by the clinic team, were excluded. Our cohort reflected the female predominance which exists in pAPS. However, patients were recruited from a single centre, there was relatively limited ethnic and gender diversity in our study population and the educational status of the participants was not recorded.

Our survey explored key factors known to influence fatigue in other RMDs, but other aspects may contribute to fatigue (e.g. physical capacity, end organ damage) and these require investigation. As data from our quantitative phase was cross-sectional, no causality can be inferred from the findings and the reciprocal effects of fatigue on other features cannot be observed (e.g. greater fatigue may lead to lower mood or less activity).

Fatigue is common and impacts the lives of adults with pAPS. Enhancing communication between patients and clinicians so that symptoms which are important to patients, such as fatigue, are identified and addressed appropriately is crucial to optimise the management of pAPS. Developing effective multidisciplinary interventions to support self-management with patients, clinicians and researchers of fatigue in people with pAPS is vital.

## ACKNOWLEDGEMENTS

The authors would like to thank APS Support UK for their financial support.

## REFERENCES

1. Cervera, R., et al., *Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients*. Annals of Rheumatic Diseases, 2015. **74**(6): p. 1011-8.
2. Myers, B. and S. Pavoud, *Diagnosis and management of antiphospholipid syndrome in pregnancy*. The Obstetrician and Gynaecologist, 2011. **13**: p. 15-21.
3. Durcan, L. and M. Petri, *Epidemiology of the Antiphospholipid Syndrome*. 2017: p. 17-30.
4. Jallow, T., D. D'Cruz, and H. Lempp, *Antiphospholipid syndrome*. British Medical Journal, 2015. **350** (h1426): p. h1426.
5. Georgopoulou, S., et al., *Antiphospholipid (Hughes) syndrome: description of population and health-related quality of life (HRQoL) using the SF-36*. Lupus, 2015.
6. Piper, B.F., *Pathophysiological Phenomena in Nursing: Human Responses to Illness*. 1993, Philadelphia, USA: WB Saunders.

7. Norheim, K.B., G. Jonsson, and R. Omdal, *Biological mechanisms of chronic fatigue*. Rheumatology, 2011. **50**(6): p. 1009-1018.
8. Hewlett S, C.Z., Byron M, Tipler S, pope D, Hehir M., *Patients' perceptions of fatigue in rheumatoid arthritis: Overwhelming, uncontrollable, ignored*. Arthritis Care & Research, 2005. **53**: p. 697-702.
9. Pettersson, S., et al., *Women's experience of SLE-related fatigue: a focus group interview study*. Rheumatology, 2010. **49**(10): p. 1935-1942.
10. Eilertsen, G., et al., *Similarities and differences in the experience of fatigue among people living with fibromyalgia, multiple sclerosis, ankylosing spondylitis and stroke*. Journal of Clinical Nursing, 2015. **24**(13-14): p. 2023-2034.
11. Primdahl, J., et al., *The Experience of people with rheumatoid arthritis living with fatigue: a qualitative metasynthesis*. BMJ Open, 2019. **9**(3): p. e024338.
12. Seifert, O. and C. Baerwald, *Impact of fatigue on rhematic diseases*. Best Practice and Research Clinical Rheumatology, 2019. **33**(3).
13. Wolfe, F., D.J. Hawley, and K. Wilson, *The prevalence and meaning of fatigue in rheumatic disease*. . Journal of Rheumatology, 1996. **23**(8): p. 1407-1417.
14. Hewlett, S., et al., *Fatigue in rheumatoid arthritis: time for a conceptual model*. Rheumatology, 2011. **50**(6): p. 1004-1006.
15. Katz, P., et al., *Role of Sleep Disturbance, Depression, Obesity, and Physical Inactivity in Fatigue in Rheumatoid Arthritis*. Arthritis Care & Research, 2016. **68**: p. 81-90.
16. Matcham, F., et al., *Psychological correlates of fatigue in rheumatoid arthritis: A systematic review*. 2015. p. 16-29.
17. Ahn, G.E. and R. Ramsey-Goldman, *Fatigue in systemic lupus erythematosus*. Int J Clin Rheumtol, 2012. **7**(2): p. 217-27.
18. Matcham, F., et al., *The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis*. Rheumatology, 2019. **52**(12): p. 2136-2148.
19. Figueiredo-Braga, M., et al., *Depression and anxiety in systemic lupus erythematosus: The crosstalk between immunological, clinical, and psychosocial factors*, in *Medicine* (Baltimore). 2018.
20. Nikolaus, S., et al., *Fatigue and factors related to fatigue in rheumatoid arthritis: a systematic review*. Arthritis care & research, 2013. **65**(7): p. 1128-1146.
21. Palagini, L., et al., *Poor sleep quality in systemic lupus erythematosus: does it depend on depressive symptoms?* Lupus, 2014. **23** (13): p. 1350-1357.
22. Manning, V.L., et al., *Are patients meeting the updated physical activity guidelines? Physical activity participation, recommendation, and preferences among inner-city adults with rheumatic diseases*. JCR: Journal of Clinical Rheumatology, 2012. **18**(8): p. 399-404.
23. Sokka, T., et al., *Physical inactivity in patients with rheumatoid arthritis: Data from twenty-one countries in a cross-sectional, international study*. Arthritis Care & Research, 2008. **59**(1): p. 42-50.
24. Mahieu, M.A., et al., *Fatigue, patient reported outcomes, and objective measurement of physical activity in systemic lupus erythematosus*. Lupus, 2016. **25**(11): p. 1190-1199.
25. Katz, P., *Causes and consequences of fatigue in rheumatoid arthritis*. Current Opinion in Rheumatology, 2017. **29**: p. 269-76.
26. Jump, R.L., et al., *Fatigue in Systemic Lupus Erythematosus: Contributions of Disease Activity, Pain, Depression, and Perceived Social Support*. Journal of Rheumatology, 2005. **32**: p. 1699-1705.
27. Tektonidou, M.G., et al., *EULAR recommendations for the management of antiphospholipid syndrome in adults*. Annals of Rheumatic Diseases, 2019. **78**(10): p. 1296-1304.
28. Creswell, J.W. and V.L. Plano Clark, *Designing and conducting mixed methods research*. 3rd ed. 2017, Los Angeles, CA: SAGE.
29. Morgan, D.L., *Practical strategies for combining qualitative and quantitative methods: application for health research*. Qualitative Health Research, 1998. **8**(3): p. 362-76.
30. Miyakis, S., et al., *International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS)*. J Thromb Haemost, 2006. **4**(2): p. 295-306.
31. Freire, P.V., et al., *Distinct antibody profile: a clue to primary antiphospholipid syndrome evolving into systemic lupus erythematosus?* Clinical Rheumatology, 2014. **33**: p. 349-353.
32. Asherson, R.A., et al., eds. *The Antiphospholipid Syndrome*. 2018, CRC Press.
33. Webster, K., D. Cella, and K. Yost, *The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation*, in *Health Qual Life Outcomes*. 2003. p. 79.

34. Lai, J.-S., et al., *Validation of the functional assessment of chronic illness therapy-fatigue scale in patients with moderately to severely active systemic lupus erythematosus, participating in a clinical trial*. The Journal of Rheumatology, 2011. **38**(4): p. 672-679.
35. Kroenke, K., R.L. Spitzer, and J.B. Williams, *The PHQ-9: validity of a brief depression severity measure*. J Gen Intern Med, 2001. **16**(9): p. 606-13.
36. Kroenke, K. and R.L. Spitzer, *The PHQ-9: A New Depression Diagnostic and Severity Measure*. Psychiatric Annals, 2002. **32**(9): p. 509-515.
37. Craig, C., et al., *International Physical Activity Questionnaire (IPAQ): 12-country reliability and validity*. Medicine Science Sports and Exercise, 2003. **35**(13): p. 81-95.
38. Buysse, D.J., et al., *The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research*. Psychiatry Res, 1989. **28**(2): p. 193-213.
39. Omachi, T.A., *Measures of sleep in rheumatologic diseases: Epworth Sleepiness Scale, functional Outcome of Sleep Questionnaire, Insomnia Severity Index and Pittsburgh Sleep Quality Index*. Arthritis Care & Research, 2011. **63**: p. S287-96.
40. Zimet, G.D., et al., *The Multidimensional Scale of Perceived Social Support*. Journal of Personality Assessment, 1988. **52**(1): p. 30-41.
41. Zimet, G.D., et al., *Psychometric characteristics of the Multidimensional Scale of Perceived Social Support*. Journal of personality assessment, 1990. **55**: p. 610-617.
42. Palinkas, L., et al., *Purposeful sampling for qualitative data collection and analysis in mixed method implementation research*. Administration and Policy in Mental Health and Mental Health Services Research, 2015. **42**(5): p. 533-44.
43. Britten, N., *Qualitative Research: Qualitative interviews in medical research*. BMJ, 1995(311): p. 251.
44. Guest, G., A. Bunce, and L. Johnson, *How many interviews are enough? An experiment with data saturation and variability*. Family Health International, 2006. **18**(1): p. 59-82.
45. Ritchie, J. and L. Spencer, *Qualitative data analysis for applied policy research*, in *Analysing qualitative data*, A. Bryman and R.G. Burgess, Editors. 1994, Routledge: London. p. 173-94.
46. Braun, V. and V. Clarke, *Using thematic analysis in psychology*. Qualitative Research in Psychology. Qualitative Research in Psychology, 2006. **3**(2): p. 77-101.
47. Seale, C., *Using computers to analyse qualitative data*, in *Doing Qualitative Research: a Practical Handbook*, D. Silverman, Editor. 1999, Sage Publications: London. p. 154-172.
48. Arnaud, L., et al., *Predictors of fatigue and severe fatigue in a large international cohort of patients with systemic lupus erythematosus and a systematic review of the literature*. Rheumatology, 2019. **58**(6): p. 987-996.
49. Loppenthin, K., et al., *Physical activity and the association with fatigue and sleep in Danish patients with rheumatoid arthritis*. Rheumatol Int, 2015. **35**(10): p. 1655-64.
50. Durcan, L., F. Wilson, and G. Cunnane, *The effect of exercise on sleep and fatigue in rheumatoid arthritis: a randomized controlled study*. Journal of Rheumatology, 2014. **41**: p. 1966-73.
51. Katz P, M.M., Gregorich S, Trupin L., *Physical Activity to Reduce Fatigue in Rheumatoid Arthritis: A Randomized Controlled Trial*. Arthritis Care & Research, 2018. **70**(1): p. 1-10.
52. Georgopoulou, S., et al., *The relationship between social support and health-related quality of life in patients with antiphospholipid (hughes) syndrome*. Modern Rheumatology, 2018. **28**(1): p. 147-155.
53. Bearne, L.M., et al., *Multidisciplinary team care for people with rheumatoid arthritis: a systematic review and meta-analysis*. Rheumatology International, 2016. **36**(3): p. 311-24.
54. McLuish. W and Bearne L. M, *Do Inpatient Multidisciplinary Rehabilitation Programmes Improve Health Status in People with long-term Musculoskeletal Conditions? A Service Evaluation*. Musculoskeletal Care, 2014.
55. National Institute for Health and Care Excellence *Rheumatoid arthritis in adults: management*. NICE Guideline. 2015 Accessed 21.05.16]; Available from: [www.nice.org.uk/guidance/cg79](http://www.nice.org.uk/guidance/cg79).



| <b>Table 1 Interview topic guide to explore the experience of fatigue in adults with primary antiphospholipid syndrome</b> |  |
|--|--|
| 1.   | Do you ever feel fatigued?   |
| 2.   | How do you feel about moving around and being active?  |
| 3.   | Tell me about your experiences of fatigue? Can you describe it to me?                            |
| 4.   | What do you think causes your fatigue?   |
| 5.   | How do the symptoms of your fatigue vary?  |
| 6.   | Does fatigue impact on your life? How?   |
| 7.   | How do you feel about your personal level of physical activity/ exercise?                        |
| 8.   | Do you manage to integrate physical activity/exercise in your daily routine?                     |
| 9.   | Do you talk to other people about your fatigue/activity levels?                                  |
| 10.  | What is your experience of talking to doctors and nurses about your fatigue?                     |
| 11.  | What is your experience of talking to doctors and nurses about your physical activity/ exercise? |
| 12.  | Have doctors or nurses suggested physical activity/ exercise as a way of managing fatigue?       |

| Table 2 Sociodemographic and clinical characteristics of adults with primary antiphospholipid syndrome   |                                    |                        |
|--|------------------------------------|------------------------|
|  | Cross-sectional survey respondents | Interview participants |
|  | Total (n=87)                       | Total (n=20)           |
| <b>Gender (female)</b>   | 79.0 (90.8)*                       | 20.0 (100)*            |
| <b>Age (years)</b>   | 50.3 (10.4)                        | 49.3 (9.7)             |
| <b>Disease duration (months)</b>   | 143.0 (92.0)                       | 149.4 (97.5)           |
| <b>Ethnicity (White British)</b>   | 75.0 (86.0)*                       | 18.0 (90.0)*           |
| <b>Registered disabled (Yes)</b>   | 13.0 (14.0)*                       | 5.0 (25.0)*            |
| <b>Employment Status</b>   | <b>Full time</b>                   | 6.0 (30.0)*            |
|  | <b>Part time</b>                   | 7.0 (35.0)*            |
|  | <b>Retired</b>                     | 2.0 (10.0)*            |
|  | <b>Unemployed</b>                  | 2.0 (10)*              |
|  | <b>Higher education</b>            | 0.0 (0.0)*             |
|  | <b>Other</b>                       | 3.0 (15.0)*            |
| <b>FS</b>  | 25.7 (13.0) <sup>b</sup>           | 24.0 (11.5)            |
| <b>PHQ-9</b>   | 9.5 (6.6)                          | 9.4 (5.2)              |
| <b>IPAQMETs</b>  | 2982.4 (3433.8) <sup>a</sup>       | 2236.3 (2540.2)        |
| <b>PSQI</b>  | 8.8 (4.6) <sup>c</sup>             | 9.3 (3.9)              |
| <b>MSPSS</b>   | 5.4 (1.4) <sup>a</sup>             | 5.2 (1.7)              |
| FS FACIT – F Fatigue subscale, IPAQMETs – International Physical Activity Questionnaire (Metabolic Equivalent of Task/minutes/week), MSPSS – The Multi-Dimensional Perceived Social Support Scale, PHQ-9 – Patient Health Questionnaire, PSQI – Pittsburgh Sleep Quality Index.<br>All mean (standard deviation) except * n(%) <sup>a</sup> n=85, <sup>b</sup> n=84, <sup>c</sup> n=71 |                                    |                        |

**Table 3 Descriptive statistics and bivariate correlations between fatigue, mood, physical activity, sleep quality, and social support in adults with primary antiphospholipid syndrome**

|          | FS | PHQ-9    | IPAQMETs | PSQI     | MSPSS   |
|----------|----|----------|----------|----------|---------|
| FS       | 1  | -0.750** | 0.232*   | -0.515** | 0.239*  |
| PHQ-9    |    | 1        | -0.105   | 0.613**  | -0.238* |
| IPAQMETs |    |          | 1        | -0.098   | 0.018   |
| PSQI     |    |          |          | 1        | -0.071  |
| MSPSS    |    |          |          |          | 1       |

\*P<0.05, \*\* P<0.01

FS – FACIT -F Fatigue subscale, IPAQMETs – International Physical Activity Questionnaire, MSPSS – The Multi-Dimensional Perceived Social Support Scale, PHQ-9 – Patient Health Questionnaire, PSQI – Pittsburgh Sleep Quality Index.

**Table 4 Backward multiple linear regression models for predicting fatigue (FS) in adults with primary antiphospholipid syndrome**

| Model          | R                  | R Square | Adjusted R Square | SE of the Estimate | F                          | p      |
|----------------|--------------------|----------|-------------------|--------------------|----------------------------|--------|
| Baseline Model | 0.762 <sup>a</sup> | 0.581    | 0.558             | 8.637              | F <sub>(4,73)</sub> =25.33 | <0.001 |
| Best Fit Model | 0.760 <sup>b</sup> | 0.577    | 0.560             | 8.622              | F <sub>(3,74)</sub> =33.65 | <0.001 |

a Predictors: IPAQMETs, PHQ-9, MSPSS, PSQI

b Predictors: IPAQMETs, PHQ-9, PSQI

FS – FACIT -F Fatigue subscale, IPAQMETs – International Physical Activity Questionnaire, MSPSS – The Multi-Dimensional Perceived Social Support Scale, PHQ-9 – Patient Health Questionnaire, PSQI – Pittsburgh Sleep Quality Index.

Table 5 Beta coefficients for the baseline model and best fit model, for predicting fatigue (FS) in adults with primary antiphospholipid syndrome

|                       |          | Unstandardized Coefficients |            | Standardized Coefficients | t      | p      | 95.0% Confidence Interval for B |             |
|-----------------------|----------|-----------------------------|------------|---------------------------|--------|--------|---------------------------------|-------------|
|                       |          | B                           | Std. Error | Beta                      |        |        | Lower Bound                     | Upper Bound |
| <b>Baseline Model</b> | PHQ-9    | -1.297                      | 0.197      | -0.655                    | -6.567 | <0.001 | -1.690                          | -0.903      |
|                       | IPAQMETs | 0.001                       | 0.0003     | 0.159                     | 2.085  | 0.041  | 0.00003                         | 0.00118     |
|                       | PSQI     | -0.317                      | 0.280      | -0.111                    | -1.132 | 0.262  | -0.876                          | 0.241       |
|                       | MSPSS    | 0.616                       | 0.716      | 0.067                     | 0.861  | 0.392  | -0.810                          | 2.042       |
| <b>Best Fit Model</b> | PHQ-9    | -1.336                      | 0.192      | -0.674                    | -6.966 | <0.001 | -1.718                          | -0.954      |
|                       | IPAQMETS | 0.001                       | 0.0003     | 0.162                     | 2.127  | 0.037  | 0.00004                         | 0.00119     |
|                       | PSQI     | -0.286                      | 0.278      | -0.100                    | -1.032 | 0.306  | -0.839                          | 0.267       |

FS – FACIT -F Fatigue subscale, IPAQMETs – International Physical Activity Questionnaire, MSPSS – The Multi-Dimensional Perceived Social Support Scale, PHQ-9 – Patient Health Questionnaire, PSQI – Pittsburgh Sleep Quality Index.